

Gut Barrier Dysfunction in Experimental Acute Pancreatitis

R Andersson,*^{MD, PhD}, X D Wang,**^{MD, PhD}

Abstract

Bacterial infections, frequently caused by bacteria of enteric origin, are often seen during the progression of severe acute pancreatitis, concomitant with the potential development of multiple organ dysfunction. In the present paper, the complex mechanisms of gut barrier dysfunction and gut origin sepsis in acute pancreatitis are discussed.

The individual parts of the gut barrier, e.g. the immunological, bacteriological and morphological (mucus, epithelium, endothelium and interstitium) components, seem to interact and depend on each other. Pancreatitis-induced hypovolaemia due to endothelial barrier leakage and gut arteriovenous shunting causes intestinal ischaemia and reperfusion injury with concomitant gut barrier dysfunction. Gut endothelial barrier dysfunction probably plays a central role. Potential molecular mechanisms could, among others, be associated with alterations in intracellular signal transduction, intercellular signalling and expression of adhesion molecules on endothelial cells.

The mechanisms underlying gut barrier dysfunction in acute pancreatitis are thus complex and still not fully elucidated. Knowledge about the regulating events will probably allow future pharmacological therapy for prevention and treatment of the severe complications of acute pancreatitis, including gut barrier dysfunction.

Ann Acad Med Singapore 1999; 28:141-6

Key words: Acute pancreatitis, Dysfunction, Endothelium, Epithelium, Gut barrier

Introduction

Bacterial infections are devastating and potentially lethal complications of acute pancreatitis, responsible for up to 80% of deaths in the condition.¹ Pathogenetic studies of acute pancreatitis imply that the disease is initially a non-bacterial insult and that secondary sepsis frequently occurs during the progression of pancreatitis, concomitant with the potential development of multiple organ dysfunction. Clinical data have demonstrated that most bacteria associated with pancreatic and peripancreatic infections are of enteric origin.^{1,3} It has been hypothesized that bacteria normally present in the gut may pass through the intestinal barrier to extraintestinal sites and the systemic circulation, and are responsible for the formation of pancreatitis-associated sepsis (gut origin sepsis). Experimental studies have shown that translocation of enteric bacteria occurred in those experimental models of acute pancreatitis which were induced by the continuous intravenous infusion of cerulein,⁴ obstruction of the common biliopancreatic duct,⁵ or intraductal injection of sodium taurodeoxycholate.⁶ This indicates that dysfunction of the gastrointestinal tract induced by acute pancreatitis may

act as both an early target of the challenge and as a factor that might exacerbate the disease, although the connecting links have not yet been identified. In the present paper, we discuss the potential mechanisms by which acute pancreatitis may influence the gut barrier function, leading to the occurrence of gut origin sepsis.

Characteristics of Gut Barrier Dysfunction

The gastrointestinal tract is a complex organ responsible for nutrient absorption and transport, hormonal production and action, and immune barrier against invasion of enteric bacteria and toxins. The function of the gastrointestinal barrier depends on the balance of the enteric bacterial ecology, mucus layer, brush border, a continuous layer of polarized, columnar epithelial cells, basement membrane, crypts, gut-associated lymphoid tissue, and capillary endothelial cells. Interaction between enteric pathogens and intestinal brush border membrane and bacterial adhesion on the membrane has been suggested to be the initial and critical step for the development of gut barrier dysfunction.⁷ The gut endothelial and epithelial barriers act as two major lines of defence to maintain the stability of both the external and

* Associate Professor
Department of Surgery
Lund University Hospital, Lund, Sweden

** Scientist
Department of Inflammation-Pharmacology
Astra Draco, Lund, Sweden

Address for Reprints: Dr Roland Andersson, Department of Surgery, Lund University Hospital, S-221 85 Lund, Sweden.

internal environments. Potential molecular mechanisms, such as cell proliferation, DNA damage, the regulation of tumour suppressor gene p53, the action of the DNA synthesis inhibitor gene p21, and the development and patterns of cell death, are involved in the maintenance of intestinal barrier homeostasis and the formation of barrier dysfunction.⁸

Gut barrier dysfunction is characterized by increased intestinal permeability and the enteric bacterial invasion through the barrier into extraintestinal sites. Pancreatitis-associated alterations in intestinal permeability have been studied by measuring both the *in vivo* leakage of isotope labelled human serum albumin from the circulation to the gut lumen and the *in vitro* mucosa to serosal transport of small molecular markers (sodium fluorescein and isotopic labelled ethylenediamine tetra-acetic acid) in the distal small intestine and colon in Ussing chambers.⁹ An increase in intestinal permeability was noted in the early stage of acute pancreatitis, probably resulting from production and release of cytotoxic oxygen-derived free radicals. Furthermore, pancreatitis-associated gut barrier dysfunction was determined by simultaneously measuring the gut endothelial barrier permeability by measuring the exudation of ¹²⁵I-labelled human serum albumin from the circulation into the gut interstitium and lumen and the gut epithelial barrier permeability as determined by the clearance of ¹³¹I-labelled human serum albumin from the gut lumen to the systemic circulation.¹⁰ The gut barrier dysfunction was measured by bacteriologically positive cultures of enteric bacteria in blood and extraintestinal tissues (bacterial translocation), and measuring pathohistological alterations.¹⁰ Data from this study demonstrated that acute pancreatitis induced an increase in both endothelial and epithelial barrier permeability, accompanied by the translocation of enteric bacteria, and intestinal mucosal damage and microcirculatory thrombosis.

Studies on acute pancreatitis-induced translocation of enteric bacteria to extraintestinal sites showed an increase with time after induction of the disease.^{6,10} The main route of bacterial translocation is through the mesenteric lymph nodes, rather than through the portal vein. The colon may be the major site of entrance for enteric bacteria to pass through the intestinal barrier. *E. coli* seems to be the predominant bacteria among the multiple populations of enteric bacteria found.

Gut Arteriovenous Shunting

Haemodynamic alterations, both systemically and locally, occur in acute pancreatitis, due to extensive loss of the circulating plasma volume and an excessive release of inflammatory mediators. Systemic arteriovenous oxygen difference was reported to decrease and pulmonary right-to-left shunting to increase in patients with necrotizing pancreatitis as compared to patients with

acute interstitial pancreatitis.¹¹ In experimental acute pancreatitis induced by retrograde intraductal injection of 5% sodium taurocholate, alterations in the pancreatitis-associated intestinal microcirculation were evaluated by measuring carbon dioxide metabolism.¹² Such carbon dioxide monitors, including carbon dioxide concentration and its increment, as well as venoarterial carbon dioxide concentration difference, reflect haemodynamic and dioxide-carbon dioxide exchange patterns both systemically and in the local microcirculation. Acute pancreatitis induced an increase in the production, release, and transport of carbon dioxide from tissues to blood both systemically and in the gastrointestinal tract. Gut arterial and venous shunting was noted after induction of acute pancreatitis as a response to hypovolaemia, resulting in an increase in carbon dioxide content in portal venous blood. The gut capacity of oxygen extraction was compromised by insufficient intestinal microcirculation. The existence of arterial and venous microcirculatory shunting in the intestine seems involved in the development of gut ischaemia and mucosal barrier failure. Further evidence to support this finding is that blood flow in intestinal arteries did not decrease after induction of acute pancreatitis, while subserosal blood flow in gut microcirculation markedly decreased during the early stage of pancreatitis.¹³ Tentative interacting mechanisms resulting in failure of the intestinal barrier are summarized in Figure 1.

Gut Endothelial Barrier Dysfunction

Endothelial cells constitute the first barrier between blood and the extravascular space, maintaining structural and functional integrity of the circulation. In addition, the numerous biological functions of the endothelial barrier include anticoagulant action, fibrinolysis, angiogenesis, synthesis and release of cytokines, expression of adhesion molecules, and regulation of vascular tone and structure. Pathophysiological changes in the endothelial barrier have been hypothesized to play an important role in the development of the systemic inflammatory response syndrome and multiple organ dysfunction syndrome.¹⁴

Endothelial barrier dysfunction is characterized by 1) loss of capillary integrity, resulting in increased capillary permeability, plasma exudation, and tissue oedema; 2) overactivation of endothelial cells, including over-production and release of cytokines, oxygen free radicals, and leukotriens; 3) hyperexpression of adhesion molecules, responsible for rolling, adhesion, and trapping of leukocytes on the surface of endothelial cells; and 4) alterations in cellular phenotypes from antithrombotic to prothrombotic. Pancreatitis-induced extrapancreatic changes are either systemic, such as hypovolaemia, hypocalcaemia, hyperglycaemia, hypertriglyceridemia, and coagulopathy, or organ-

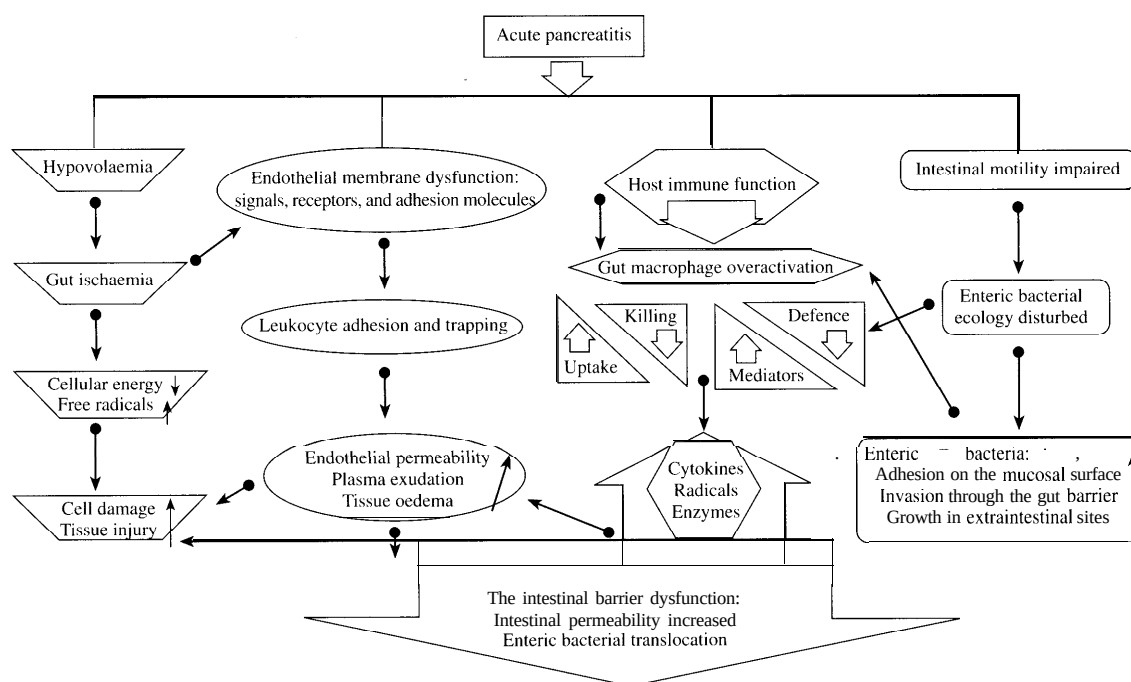


Fig. 1. Tentative interacting mechanisms resulting in failure of the intestinal barrier in acute experimental pancreatitis

specific dysfunction, including pulmonary failure, cardiovascular disturbance and renal insufficiency, potentially resulting in the development of the multiple organ dysfunction syndrome.¹⁵ In experimental acute pancreatitis, an increase in endothelial barrier permeability occurred in the gastrointestinal tract, peritoneum, pancreatitis, kidneys, liver, lungs and heart, followed by organ dysfunction, such as hepatocyte damage, elevated plasma levels of pancreatic enzymes, compromised renal function, and delayed intestinal motility.¹⁶ This implies that pancreatitis-associated endothelial barrier dysfunction is involved in the development and formation of pancreatitis-associated multiple organ system failure. The variation of endothelial barrier resistance in multiple organs appeared to be organ/tissue-dependent and also depending on challenge and time/duration as seen in animals with either septic or non-septic challenges.¹⁷ Such organ/tissue-dependent variation in endothelial barrier resistance even exists in normal animals. This indicates that the organ/tissue-dependent variation of endothelial barrier resistance may be responsible for the sequence by which multiple organ dysfunction develops. In experimental acute pancreatitis, the endothelial barrier resistance was constantly lower in the peritoneum, pancreas, colon, lungs, and kidneys.

Endothelial barrier dysfunction also contributes to the development of gut barrier dysfunction. Evidence to support this is that intravenous pretreatment with antioxidants prevented gut endothelial barrier dysfunction, followed by improving alterations in intestinal permeability, D-xylose absorption from the gut lumen to

the portal vein, and the delayed intestinal motility.^{9,16} To clarify the role of gut endothelial and epithelial barrier dysfunction in the development of gut barrier dysfunction, the functions of both the endothelial and epithelial barriers were simultaneously monitored by measuring the bidirectional barrier permeability in an in situ isolated intestinal loop connected with a luminal perfusion system in a model of individual barrier compromise induced by intravenous (for endothelial injury) or gut luminal administration (for epithelial damage) of detergents.¹⁸ This study showed that epithelial barrier dysfunction and alterations in epithelial microvilli were dependent on the dose of intraluminal detergent and only high doses could cause endothelial barrier dysfunction, while endothelial barrier dysfunction induced by intravenous administration of detergents was always accompanied with epithelial barrier dysfunction. This illustrates that the gut endothelial barrier integrity plays an important and central role for the maintenance of normal intestinal barrier function. Gut endothelial barrier dysfunction may thus initiate the development of both epithelial and total gut barrier dysfunction.

Intercellular Signals

Oxygen Free Radicals

Oxygen free radicals, such as superoxide anion free radicals, hydrogen peroxide, hydroxyl radicals, and hypochlorous acid, play an important role in the pathogenesis of endothelial barrier dysfunction in multiple organs/tissues after various challenges.¹⁴ Oxidative stress might be an early phenomenon in acute experi-

mental pancreatitis.¹⁹ Enhanced generation of oxygen free radicals exacerbates pancreatic tissue damage and extrapancreatic organ failure. Oxygen free radicals act both as cytotoxins directly compromising cell damage and as intercellular signals regulating inflammatory reactions. Intravenous pretreatment with the hydroxyl radical (dimethylsulfoxide) and hydrogen peroxide scavengers (N-acetyl-L-cysteine) prevented against the otherwise occurring increase in intestinal permeability, compromised gut absorption, and delayed motility in acute experimental pancreatitis.^{9,16}

Intracellular Calcium

Cytosolic calcium, as a critical second messenger on the cellular membrane, is involved in the regulation of endothelial barrier function and transendothelial resistance.²⁰ Intravenous pretreatment with verapamil and diltiazem, blockers for the α_1 subunit of the L-type slow calcium channels, partially prevented pancreatitis-induced endothelial barrier dysfunction in some organs/tissues in an organ/tissue-dependent fashion.¹⁶ Different calcium channels appear to play various roles in the pathogenesis of endothelial barrier dysfunction. In the development of gut endothelial barrier dysfunction induced by acute pancreatitis, the benzothiapine-type calcium channel responsible for mitochondrial sodium-calcium exchange seemed more important than the phenylalkylamine-type calcium channel responsible for the complete depletion of the extramitochondrial calcium stores.

Interleukins

Alterations in cytokine levels have been suggested to be essential in the pathogenesis of both the local and systemic inflammatory response in acute pancreatitis.²¹ Elevated tissue-specific proinflammatory cytokines during experimental acute pancreatitis may be an important mechanism for pancreatitis-associated multiple organ failure.²² It is possible that cytokines produced and released from the leukocyte system (e.g. leukocytes, endothelial cells, mast cells, and platelets) act as intercellular signals, inducing distant organ/tissue compromise during acute pancreatitis. For example, tumour necrosis factor- α (TNF) and interleukin-1- β (IL-1) mRNA and proteins were primarily noted within the pancreas at the early stage of experimental pancreatitis, followed by their production in the lungs, liver, and spleen.² Furthermore, increased plasma levels of TNF and IL-1 were detected 1 and 3 hours after induction of acute pancreatitis, followed by the development of pulmonary endothelial barrier and pneumocyte injury as well as gut barrier dysfunction.²³

Platelet-activating Factor

Platelet-activating factor (PAF), with an O-alkyl ether residue at the *sn*-1 position, a short acyl chain at *sn*-2

position, and a polar head group O-phosphocholine at *sn*-3 position, is one of those inflammatory mediators, synthesized, released and regulated mainly by the leukocyte system. PAF is involved in inflammatory responses by PAF receptor-mediated transmembrane signalling mechanisms.²⁴ Experimental studies have demonstrated that both systemic endogenous and local pancreatic PAF levels were increased after induction of acute pancreatitis.²⁵ Clinical studies showed that administration of a PAF antagonist reduced the incidence of organ dysfunction and suppressed the levels of interleukins and proteinases in human acute pancreatitis.²⁶ We found that blocking of PAF prevented the occurrence of pancreatitis-associated gut barrier dysfunction measured by gut origin sepsis and bidirectional permeability of the intestinal barrier as well as microthrombosis in intestinal villi.¹⁰ It is possible that PAF may play an important role in the pathogenesis of pancreatitis-associated gut barrier dysfunction and in the development of distant organ dysfunction by triggering endothelial barrier dysfunction. PAF may also act, at least partially, as a coordinator with other cytokines, involving leukocyte adhesion on the endothelial surface and transmigration of leukocytes from the circulation to the intestinal interstitium, since we noted that the PAF antagonist could partially reduce plasma levels of IL-1 and intestinal myeloperoxidase activity after induction of acute pancreatitis.²⁷

Potential mechanisms by which intercellular signals are produced and involved in pancreatitis-associated gut barrier dysfunction include that acute pancreatitis may initiate overactivation of the leukocyte system in the pancreas and the circulation, producing intercellular signals resulting in overactivation of the intestinal leukocytes and inflammatory reactions, or pancreatitis-induced systemic alterations (e.g. ischaemia/reperfusion) that simultaneously cause overactivation of the leukocyte system both in the circulation and other distant organs (including the intestine).

Adhesion Molecules on the Endothelial Barrier

Although the understanding that variation of endothelial barrier resistance depends on organ/tissue, time, and challenge¹⁷ provides a possible explanation for the sequence of development of multiple organ dysfunction, the mechanisms by which such variation and dysfunction occur during acute pancreatitis are still obscure. One possible explanation is that the exposure of adhesion molecules on the surface of endothelial cells may regulate variation of endothelial barrier resistance. For example, regional variation in endothelial adhesion molecule expression was noted among organs/tissues and such organ-dependent variation was referred with the differences in endothelial cell surface area among organs/tissues by comparing intercellular cell adhesion

molecule expression per unit endothelial cell surface area.²⁸ Exposure of adhesion molecules on the endothelial surface can slow down circulating leukocytes and provide possibilities for leukocyte rolling, adhesion, and trafficking to extravascular locations, resulting in the development of tissue inflammation, cell damage, and organ dysfunction.

It is hypothesized that over-expression of intestinal endothelial adhesion molecules may be involved in the pathogenesis of pancreatitis-associated gut barrier dysfunction. To evaluate this hypothesis, monoclonal antibodies against two critical adhesion molecules, intercellular cell adhesion molecule-1 (ICAM-1) and platelet/endothelial cell adhesion molecule-1 (PECAM-1), were administered intravenously prior to induction of acute pancreatitis by taurodeoxycholate in the rat. Endothelial ICAM-1 is responsible for activation-dependent attachment of integrins on leukocytes to perform the firm or secondary cell adhesion to the endothelium, and PECAM-1 expressed at endothelial cell junctions appears to be essential for transmigration binding homophilically to PECAM-1 expressed on leukocytes.²⁹ Our preliminary data demonstrate that blocking of PECAM-1 suppressed the systemic levels of cytokines, prevented the occurrence of intestinal endothelial barrier dysfunction, and reduced leukocyte trapping into the mucosal extravascular space. Blocking ICAM-1 on the other hand showed a less preventive effect than anti-PECAM-1. This indicates that leukocyte trapping in extravascular sites may be important in the development of pancreatitis-associated gut barrier dysfunction. Another possibility is that the anti-PECAM-1 effect may be carried out both on the endothelial and leukocyte surfaces, resulting not only in a reduction of leukocyte transmigration, but also decreasing leukocyte rolling on the endothelial surface during the initial phase of leukocyte-endothelial interaction and preventing against leukocyte overactivation by blocking PECAM-1 on the leukocyte surface.

Hypothesis on Signal Transduction

Both clinical and experimental studies have illustrated that acute pancreatitis is a multiple organ dysfunction syndrome, with infectious complications caused by bacteria and their toxins and increased concentrations of signalling molecules (e.g. cytokines) as mentioned above. Most of these signalling molecules induce cellular responses by binding to specific cell-surface receptors. Structural and biochemical changes of these receptors can then be transmitted to the interior of the cell. The signal transduction, an extracellular signal-membrane receptor-intracellular target interaction, then initiates the synthesis of new proteins through alterations in the pattern of gene expression. Nuclear factor kappa B (NF- κ B) is one important and widely used transcription

factor for regulating many cellular responses to environmental changes during many immune and inflammatory reactions.^{30,31} It is possible that pancreatitis-induced over-production of intercellular signals and secondary bacterial infection activate interleukin-1 receptor-related membrane signalling, inducing cytoplasmic NF- κ B which is then transported into the nucleus and binds to promoter areas of genes, and a class of inhibitory proteins (IkBs), causing endothelial cell overactivation. Such overactivation may then result in exposure of endothelial adhesion molecules, leukocyte-endothelial interaction, and endothelial barrier dysfunction.

In conclusion, gut origin sepsis is a potential mechanism of secondary bacterial infection in acute pancreatitis, probably contributing to the development of the multiple organ dysfunction syndrome. Pancreatitis-induced gut arteriovenous shunting causes intestinal ischaemia and reperfusion, followed by gut barrier dysfunction. Gut endothelial barrier dysfunction is a central link in the development and formation of gut barrier dysfunction during acute pancreatitis. Potential molecular mechanisms by which acute pancreatitis initiates the development of gut barrier dysfunction could be associated with alterations in intercellular signals, adhesion molecules, and intracellular signal transduction. Future pharmacological therapies should be focused on prevention and blocking of these major changes in order to improve patient outcome from acute pancreatitis-associated multiple organ dysfunction.

REFERENCES

1. Lumsden A, Bradley III E L. Secondary pancreatic infections. *Surg Gynecol Obstet* 1990; 81:180-91.
2. Beger H G, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. *Gastroenterology* 1986; 91:433-41.
3. Bradley E L, Aller K. A prospective longitudinal study of obstruction versus surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 1991; 161:19-21.
4. Medich D S, Lee T K, Melhem M F, Rowe M I, Schraut W H, Lee K K W. Pathogenesis of pancreatic sepsis. *Am J Surg* 1993; 165:46-56.
5. Runkel N F, Moody F G, Smith G S, Rodriguez L F, LaRocco M T, Miller T A. The role of the gut in the development of sepsis in acute pancreatitis. *J Surg Res* 1991; 51:18-22.
6. Wang X D, Andersson R, Soltesz V, Leveau P, Ihse I. Gut origin sepsis, macrophage function, and oxygen extraction associated with acute pancreatitis in the rat. *World J Surg* 1996; 20:299-308.
7. Wang X D, Andersson R. Intestinal brush border membrane function. *Scand J Gastroenterol* 1994; 29:289-99.
8. Andersson R, Wang X D, Soltesz V. The significance and potential molecular mechanisms of gastrointestinal barrier homeostasis. *Scand J Gastroenterol* 1997; 32:1073-82.
9. Wang X D, Wang Q, Andersson R, Ihse I. Alterations in intestinal function in acute pancreatitis in an experimental model. *Br J Surg* 1996; 83:1537-42.

10. Andersson R, Wang X D, Sun Z W, Deng X M, Soltesz V, Ihse I. The effect of a platelet-activating factor antagonist on pancreatitis-associated gut barrier dysfunction in rats. *Pancreas* 1998; 17:107-19.
11. Oettinger W, Beger H G. Hemodynamic changes in acute pancreatitis. In: Beger H G, Buchler M, editors. *Acute Pancreatitis*. Berlin: Springer-Verlag, 1987:207-10.
12. Wang X D, Andersson R, Kruse P, Ihse I. Carbon dioxide transport in rats with acute pancreatitis. *Int J Pancreatol* 1996; 19:103-12.
13. Andersson R, Wang X D, Ihse I. The influence of abdominal sepsis on acute pancreatitis in rats: A study on mortality, permeability, arterial pressure, and intestinal blood flow. *Pancreas* 1995; 11:365-73.
14. Wang X D, Andersson R. The role of endothelial cells in the systemic inflammatory response syndrome and multiple system organ failure. *Eur J Surg* 1995; 161:703-13.
15. MacFadden D W. Organ failure and multiple organ system failure in pancreatitis. *Pancreas* 1991; 6:S37-S43.
16. Wang X D, Deng X M, Haraldsen P, Andersson R, Ihse I. Antioxidant and calcium channel blockers counteract endothelial barrier injury induced by acute pancreatitis in rats. *Scand J Gastroenterol* 1995; 30:1129-36.
17. Deng X M, Wang X D, Andersson R. Endothelial barrier resistance in multiple organs after septic and nonseptic challenges in the rat. *J Appl Physiol* 1995; 78:2052-61.
18. Sun Z W, Wang X D, Deng X M, Wallen R, Gefors L, Hallberg E, et al. The influence of circulatory and gut luminal challenges on bidirectional intestinal barrier permeability in rats. *Scand J Gastroenterol* 1997; 32:995-1004.
19. Dabrowski A, Gabryelewicz A. Oxidative stress. An early phenomenon characteristic of acute experimental pancreatitis. *Int J Pancreatol* 1992; 12:193-9.
20. Lum H, Aschner J L, Philips PG. Time course of thrombin-induced increase in endothelial permeability: relationship to Ca_i^{2+} and inositol polyphosphates. *Am J Physiol* 1992; 263:L219-L225.
21. Kingsnorth A. Role of cytokines and their inhibitors in acute pancreatitis. *Gut* 1997; 40:1-4.
22. Norman J G, Fink G W, Denham W, Yang J, Carter G, Sexton C, et al. Tissue-specific cytokine production during experimental acute pancreatitis: A probable mechanism for distant organ dysfunction. *Dig Dis Sci* 1997; 42:1783-8.
23. Wang X D, Börjesson A, Sun Z W, Wallen R, Deng X M, Zhang H Y, et al. The association of type 11 pneumocytes and endothelial permeability with the pulmonary custocyte system in experimental acute pancreatitis. *Eur J Clin Invest* 1997; 27:936-42.
24. Chao W, Olson M S. Platelet-activating factor: receptors and signal transduction. *Biochem J* 1993; 292:617-29.
25. Zhou W, Levine B A, Olson M S. Platelet-activating factor: A mediator of pancreatic inflammation during cerulein hyperstimulation. *Am J Pathol* 1993; 142:1504-12.
26. Kingsnorth A N, Galloway S W, Formela L J. Randomized, double-blind phase II trial of lexipafant, a platelet-activating factor antagonist, in human acute pancreatitis. *Br J Surg* 1995; 83:1414-20.
27. Wang X D, Sun Z W, Börjesson A, Andersson R. Inhibition of platelet-activating factor, intercellular adhesion molecule-1, and plate endothelial cell adhesion molecule-1 reduces pancreatitis-associated gut endothelial dysfunction in rats. *Br J Surg* 1999 (In press).
28. Panes J, Perry M A, Anderson D C, Maning A, Leone B, Cepinskas G, et al. Regional differences in constitutive and induced ICAM-1 expression in vivo. *Am J Physiol* 1995; 269:H1955-H1964.
29. Newman P J. The biology of PECAM-1. *J Clin Invest* 1997; 99:3-8.
30. Baeuerle P A, Baltimore D. NF- κ B: ten years after. *Cell* 1996; 87:13-20.
31. Baldwin A S. The NF- κ B and I κ B proteins: new discoveries and insights. *Annu Rev Immunol* 1996; 14:649-83.